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OBSERVATIONS ON THE OPSONIC INDEX AND THE ANTIPNEUMOCOCCAL POWER OF THE BLOOD IN PNEUMONIA.*

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It has been shown by Wright and Douglas and others that phagocytosis of various bacteria is dependent upon the presence in the blood and other fluids of certain substances called opsonins; moreover, that these substances exert their influence upon the bacteria and not directly upon the leucocytes. It has been demonstrated also that opsonins are increased during the course of acute infections, especially as recovery takes place, and that they may be artificially increased by the injection of killed bacteria. Thus Wright and Douglas¹ have shown that there may be a deficiency of the proper opsonins in chronic staphylococcus infections and in tuberculosis, and that the opsonins are increased by injection of corresponding bacterial vaccines. Mennes² previously described an increase in the substance that promotes phagocytosis of pneumococci in the serum of animals immunized to pneumococci. He took the view then prevalent that the substance in question acted wholly by stimulating the leucocytes to phagocytic action. Hektoen³ obtained increase in the streptococcic opsonic index in man by the injection of dead streptococci, while Neufeld and Rimpau⁴ found that sera of animals immunized to streptococci and pneumococci prepare virulent strains of these bacteria for phagocytosis, while normal sera do not.

It was thought, therefore, that it would be of interest to determine the opsonic power of the blood during the course of pneumonia in its various phases. Corresponding dilutions of normal and pneumonic serum were added to fixed quantities of washed blood (leuco-

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¹ References to the work of Wright and his colleagues are given by Wright, *Lancet*, 1905, 2, p. 1598.

² *Zeitschr. f. Hyg.*, 1897, 25, p. 413.

³ *Jour. Am. Med. Assoc.*, 1906, 46, p. 1407.

⁴ *Deutsch. med. Wchnschr.*, 1904, 32, p. 1459.

cytes) and pneumococcal suspension with the view of eliciting minute variations in the resulting phagocytosis. The quantities of 0.2, 0.1, 0.05, 0.025, 0.0125 c.c. of serum were tried, the quantity in each instance being made up to 0.2 c.c. and each tube contained in addition 0.2 c.c. of washed normal blood (leucocytes) and 0.2 c.c. of pneumococcus N suspended in normal salt solution. Pneumococcus N was isolated from the blood of a pneumonia patient three months before, and is quite readily taken up by the leucocytes under these circumstances. The mixtures were incubated at 37° C., and at the end of 20 minutes smears were made and stained, the number of organisms counted in at least 20 leucocytes in each case, and an average obtained. It was found that 0.025 c.c. gave the most satisfactory results, and the pneumococco-opsonic indexes in the charts are based on results so obtained.

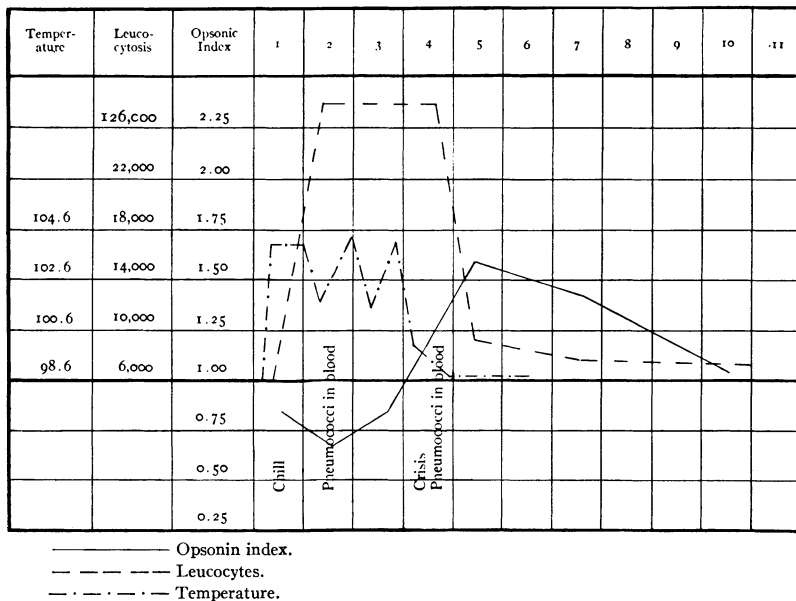
Eleven cases were studied by this method, usually with daily determinations before crisis in typical cases, and less frequently thereafter. This series includes two cases of pneumococcal empyema and two cases of migratory pneumonia, two fatal cases of pneumonia, while the remaining five were cases of typical lobar pneumonia terminating in crisis. Besides the determination of the opsonic index, leucocyte counts and blood cultures were made, the results of which are indicated also in the charts.

All the typical cases of pneumonia were found to have certain characteristics in common, and Chart 1 illustrates the type of variation in the pneumococco-opsonic index in typical pneumonia with definite crisis. It is noteworthy that the opsonic index persists below normal until within a few hours before crisis (the negative phase of Wright), then it rises above normal and reaches its height within 24 hours after crisis when decline toward normal takes place. The leucocyte curve, on the other hand, rises rapidly after the chill and begins to decline as the opsonic index rises remaining above normal for a few days after crisis.

While the opsonic index may be regarded as an index of the protective powers of the blood we must not leave out of sight the rôle of the polymorphonuclear leucocytes which are equally necessary for phagocytosis. As the leucocytes are enormously increased in pneumonia the antipneumococcal power of the blood may be much

greater than is apparent from the study of the opsonic curve only. If each leucocyte in normal serum takes up 4 pneumococci and there are 4,200 such polynuclear leucocytes per c.mm. of normal blood, we may consider that $4,200 \times 4 = 16,800$ organisms might be taken up in each c. mm. of blood. If 3 pneumococci are taken up by each pneumonic leucocyte in pneumonic serum during the negative phase and there are 18,700 leucocytes per c.mm., the total number of organisms taken up will be $3 \times 18,700 = 56,100$, which would represent the entire antipneumococcic power of 1 c.mm. of pneumonic

CHART 1.
PNEUMOCOCCO-OPSONIC INDEX IN TYPICAL PNEUMONIA ENDING IN CRISIS.



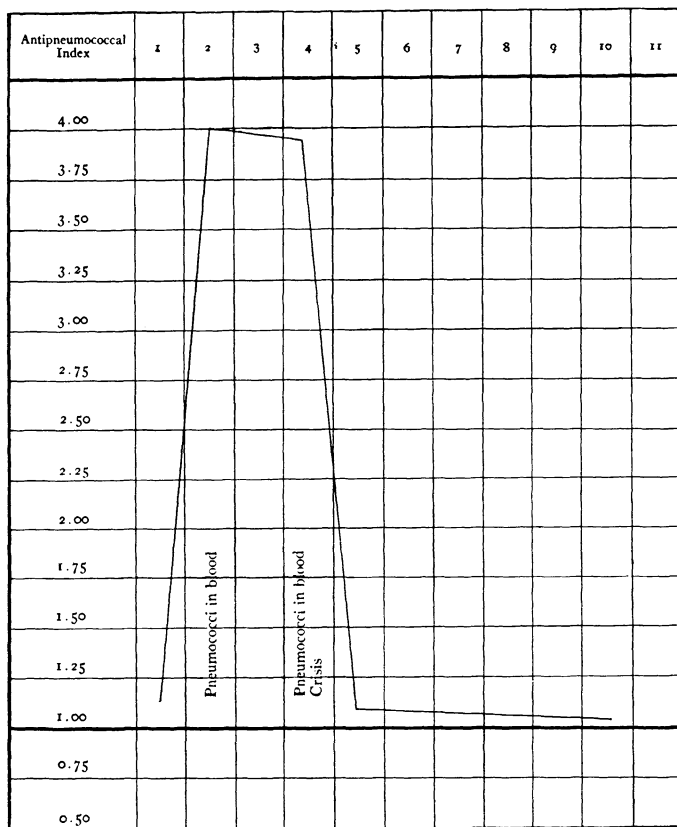
blood. It is therefore readily seen that although the pneumococco-opsonic index of pneumonic blood may be below normal early in pneumonia, the antipneumococcal power of the same may be $3\frac{1}{2}$ times the normal, assuming of course that the opsonin present is sufficient to opsonize the quota of pneumococci necessary. It is noteworthy that Rosenow's¹ observations upon the rôle of polymorphonuclear leucocytes in the pneumococcal action of human blood *in vitro* go to support the view here taken.

¹ *Jour. Infect. Dis.*, 1906, 3, p. 683.

This possible relative antipneumococcal value of the blood of a typical case of pneumonia (Chart 1) I have plotted on Chart 2, from which we see that although the pneumococco-opsonic index (Chart 1) is below normal during the first two days, the actual anti-pneumococcal power would be far above normal. This relation appears to

CHART 2.

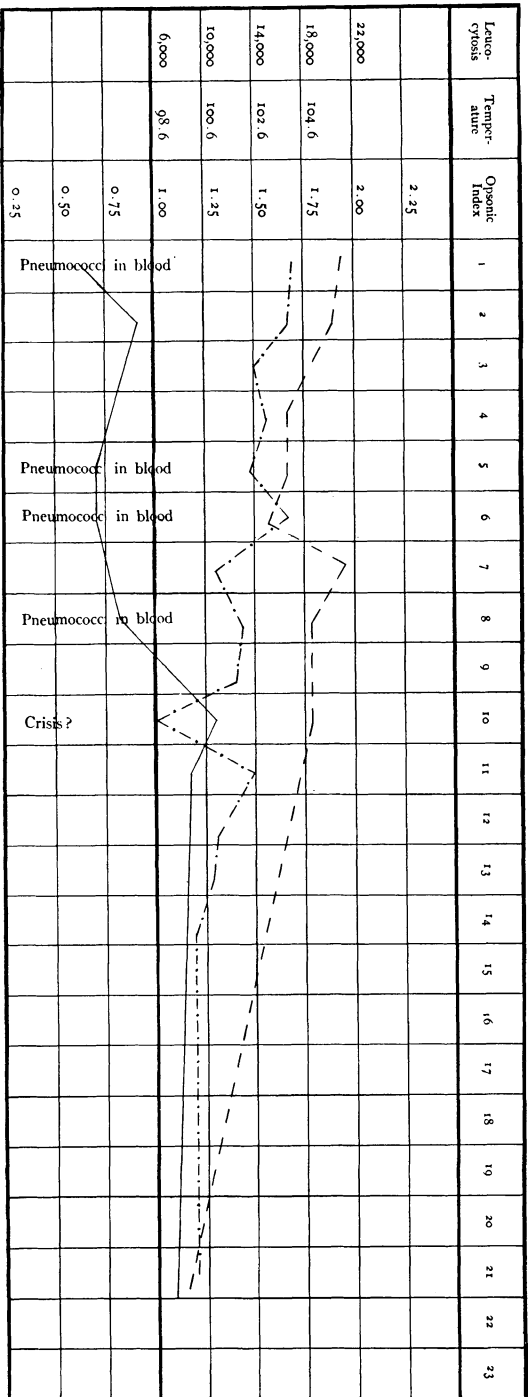
ANTIPNEUMOCOCCAL POWER OF THE BLOOD IN A TYPICAL CASE OF PNEUMONIA.



continue until the opsonins are at their height, i. e., shortly after crisis, when the leucocytes have so decreased that the antipneumococcal power of the blood would be decidedly lowered though still above normal. The highest point reached thus appears to be shortly before crisis is complete.

CHART 3.

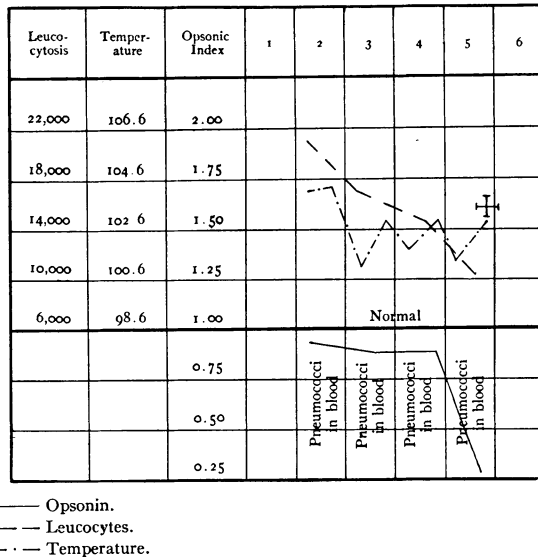
OPSONIN, LEUCOCYTE, AND TEMPERATURE CURVES IN A CASE OF MIGRATORY PNEUMONIA.



————— Opsonin.
 - - - - - Leucocytes.
 - . - . - Temperature.

Two cases of migratory pneumonia were studied and the conditions are illustrated in Chart 3. This particular case was first seen on its fourth day after the chill, when the opsonic index was below normal, rising somewhat the next day. Then extension of the process in the lung took place, three lobes becoming successively involved, the pneumococco-opsonic index declining. On the twelfth day of the attack the opsonins rose above normal and reached their height on the next day when the temperature became normal for the first time. There was delayed resolution and slight fever until

CHART 4.
PNEUMOCOCCO-OPSONIC INDEX IN FATAL PNEUMONIA.



the 25th day, when resolution become complete. During this time the opsonic index remained above normal.

It is interesting that in the fatal cases examined the opsonic index continued to fall until death. In the case represented on Chart 4 considerable leucocytosis was present and the total anti-pneumococcal power might be conceived as still considerably above normal. It is of interest to note that the number of leucocytes was falling steadily. In other cases with a decided hypoleucocytosis and a low pneumococco-opsonic index the total antipneumococcal

power would certainly be low and perhaps explain, to some extent, the fatal results, though many more cases must be examined before definite conclusions may be drawn.

Opsonins in metapneumonic pleuritic and arthritic exudates.—The pus from four cases of postpneumonic empyema and one case of pneumococcal arthritis was obtained and centrifugated. The supernatant fluid so obtained was found to be devoid of opsonins. Varying quantities of this fluid were added to washed human corpuscles (leucocytes), normal and suspensions of organisms in order to test whether it possessed antileucocytic and antiphagocytic power. Table 1 shows that these fluids have no power to suspend phagocytosis.

TABLE 1.
INFLUENCE OF PNEUMOCOCCAL EXUDATES ON PHAGOCYTOSIS.

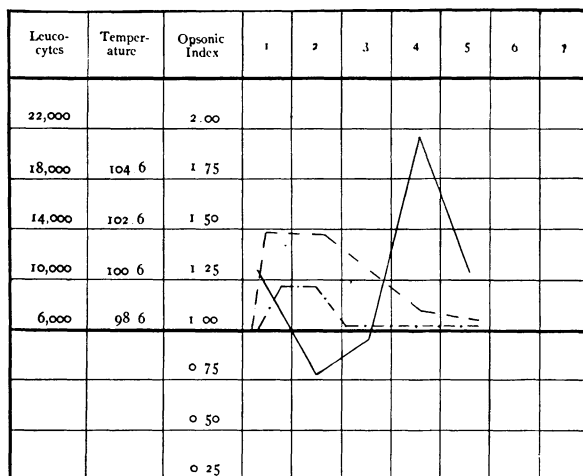
MIXTURES	PHAGOCYTOSIS	
	20 Min.	1 Hr.
Pleuritic exudate 0.4 c.c. + washed corpuscles 0.2 c.c. + serum 0.2 c.c. + suspension 0.2 c.c.	4	10
Pleuritic exudate 0.2 c.c. + washed corpuscles 0.2 c.c. + serum 0.2 c.c. + suspension 0.2 c.c.	6	9.8
Normal salt solution 0.4 c.c. + washed corpuscles 0.2 c.c. + serum 0.2 c.c. + suspension 0.2 c.c.	4	11
Normal salt solution 0.2 c.c. + washed corpuscles 0.2 c.c. + serum 0.2 c.c. + suspension 0.2 c.c.	6	10.2
Pleuritic exudate 0.2 c.c. + washed corpuscles + suspension 0.2 c.c.	0	0

Production of immune opsonins by injection of pneumococcal vaccines.—It has already been mentioned that the opsonins in the blood may be increased by the injection of bacterial substances or vaccines (Wright). The following experiment may be given as a further illustration: A healthy man was injected under the skin of the arm with the 24-hour growth of 10 blood-agar slants of virulent pneumococcus S heated to 60° C. for one hour. This was followed in four hours by a leucocytosis of 13,800 persisting for 48 hours together with slight rise in temperature as shown in Chart 5. There were also some malaise and headache, while locally there was considerable pain, reddening, and infiltration which disappeared without softening in 48 hours. The general symptoms also subsided within 36 hours.

The train of events as seen from Chart 5 correspond well with the changes that occur in cases of pneumonia—at first there is a

CHART 5.

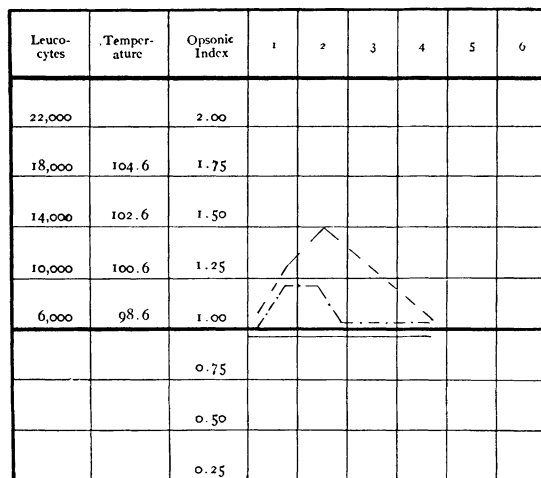
INFLUENCE OF DEAD VIRULENT PNEUMOCOCCI UPON THE OPSONIC INDEX IN A NORMAL INDIVIDUAL.



———— Opsonin.
 - - - - - Leucocytes.
 - Temperature.

CHART 6.

INFLUENCE OF DEAD AVIRULENT PNEUMOCOCCI UPON THE OPSONIC INDEX OF A NORMAL INDIVIDUAL.



———— Opsonin.
 - - - - - Leucocytes.
 - Temperature.

rapid decrease in opsonins, followed by rapid rise with a decline to normal. It is to be noted that the leucocytes here also begin to drop as the opsonins rise.

As it had been noted that dead avirulent pneumococci produce as marked a temperature and leucocyte reaction as do dead virulent cultures, another experiment was made in which dead avirulent pneumococci were substituted for the virulent ones. The result is shown in Chart 6. The temperature and leucocyte reactions are comparable to those in the experiment with virulent pneumococci but no appreciable difference was exerted upon the pneumococco-opsonic index. Now we know that virulent pneumococci, dead or alive, *in vitro* are not susceptible to phagocytosis in normal or pneumonic blood. It is therefore possible that the property of virulence is concerned in stimulating the production of immune opsonins observed in Chart 5 but lacking in Chart 6.

Effect of pneumococcal vaccines in pneumonia.—It has been found that opsonins can be increased by injections of the proper bacterial vaccines and that this increase is in many cases associated with a favorable influence upon the infection. Whether this salutary effect can be explained wholly by the increase in opsonins, as some are inclined to think, is perhaps questionable, yet the opsonic index certainly may be taken as a sort of measure of the resistance as shown from the foregoing observations.

In all, 14 cases of lobar pneumonia were treated by the injections of pneumococcal vaccines, of which 11 recovered and 3 ended fatally, as indicated in Table 2. In all cases with a favorable termination there was a very slight rise of temperature from four to six hours after the injection together with an increased leucocytosis. Crisis also occurred from 18 to 36 hours after the injection in all but one case, where a second injection was given and crisis took place 18 hours after the last injection. The opsonins, below normal at the first determination, rose characteristically just before crisis, though no exaggeration of the negative phase occurred immediately after the injections. In other words, the evolution of the course was precisely that of a case untreated, with the exception that crisis seemed to occur early. In the 11 cases that recovered, five cases had the crisis on the third day, three on the fourth, one on the fifth, and two

on the sixth. These cases were chosen at random from cases with a mortality of about 40 per cent for that month; hence the number of recoveries among the injected would seem to be high, and certainly crisis occurred unusually early.

TABLE 2.
EFFECT OF INJECTIONS OF PNEUMOCOCCAL VACCINES IN PNEUMONIA.

PATIENT	DAY OF DISEASE	LEUCOCYTES		TEMPERATURE		CRISIS OR DEATH			INVOLVEMENT
		Before Injection	Four hrs. after Injection	At Injection	Four hrs. after Injection	Result	Day of Disease	After Injection	
F. G.	3d	19,200	30,000	103.4	103.8	Crisis	4th	34 Hrs.	L. l. lobe
A. B.	3d	17,200	24,000	102.2	102.6	"	4th	26 "	R. l. lobe
A. E. B.	2d	101.2	101.8	"	3d	40 "	R. l. and r. m. lobes
J. C.	2d	101.4	101.8	"	3d	24 "	Rt. side complete
M. D.	3d	27,100	28,000	102.2	102.2	"	4th	22 "	R. l. lobe
Sch.	4th	37,000	38,000	103.0	103.4	"	5th	24 "	L. l. lobe
P. K.	6th	25,500	26,500	102.8	103.0	"	6th	18 "	R. l. and r. m. lobes
A. S.	3d	12,000	18,000	102.0	102.4	"	3d	16 "	L. l. lobe
T. M.	2d, 3d	22,600	29,000	103.0	103.4	"	6th	30 "	Complete rt. side
A. B.	2d	19,200	26,000	102.6	103.2	"	3d	36 "	L. l. lobe
A. H.	2d	14,000	20,000	103.0	103.4	"	3d	26 "	L. l. lobe
L. W.	2d	17,000	14,000	102.2	102.0	Death	6th	96 "	Rt. upper and mid. and l. l. lobes
A. H.	4th	14,000	12,250	101.2	101.0	"	5th	18 "	Complete l. lung
C. H.	3d	4,000	3,100	103.8	103.6	"	5th	42 "	Rt. u. and m. lobes

Of the three cases ending fatally two were senile pneumonias, while the other showed a marked hypoleucocytosis. In these cases after injection no marked temperature or leucocyte reaction occurred, nor was it followed by any increase or decrease in opsonins. This condition of affairs might be construed to mean that the sources of vital resistances of the body had been so thoroughly exhausted as to permit of no further stimulation.

SUMMARY AND CONCLUSIONS.

1. In pneumonia the pneumococco-opsonic index is first decreased, but rises in favorable cases, reaching its height soon after crisis, while in fatal cases it remains persistently low.
2. The estimated total antipneumococcal index (estimated from the leucocytic index and the opsonic index) is early increased and remains high until crisis is complete in cases with favorable termination.
3. Pneumococcal exudates contain little or no pneumococco-opsonin nor do they exert any antiphagocytic action.

4. Dead virulent pneumococci produce a similar evolution in the antipneumococcal index in normal persons to that which occurs in pneumonia.

5. Dead avirulent pneumococci have no effect on the pneumococco-opsonins.

6. Treating patients with lobar pneumonia with pneumococcal vaccines seems to exert a favorable influence upon the course of the disease, as indicated by an apparent decrease in mortality and by early crisis, but a great deal of further work is necessary before any conclusions of final value may be drawn.

I herewith wish to express my thanks to the Rush Alumni Association, for making the work possible; to Dr. Hektoen, under whose direction it was done; and to the house staff of the Cook County Hospital for the many courtesies shown.